

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrADTRALZA®

Tralokinumab injection

Single-use pre-filled syringe (150 mg/1 mL)

Single-use pre-filled pen (300 mg/2 mL)

Solution for subcutaneous injection

Immunomodulator, Interleukin inhibitor
ATC Code: D11AH07

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ADTRALZA (tralokinumab injection) is indicated for the treatment of moderate-to-severe atopic dermatitis in adult and adolescent patients 12 years and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Adtralza can be used with or without topical corticosteroids.

1.1 Pediatrics

Pediatrics (< 12 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use in patients <12 years of age.

1.2 Geriatrics

Geriatrics (≥ 65 years): Of the 1605 patients exposed to Adtralza in the initial 16-week treatment period of 5 atopic dermatitis clinical studies in adults, a total of 77 patients were ≥ 65 years of age. Although the number of patients aged 65 and over is limited, evidence from clinical studies suggests there are no differences in safety and efficacy between older and younger subjects. No dose adjustment is recommended for elderly patients.

2 CONTRAINDICATIONS

- Tralokinumab injection is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see [\(6\)](#) DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the product monograph.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Adtralza can be used with or without topical corticosteroids. Adtralza may be used with topical calcineurin inhibitors.
- Health Canada has not authorized an indication for pediatric use in patients < 12 years of age as no data are available for this age group [see [\(1.1\)](#) INDICATIONS, Pediatrics].

4.2 Recommended Dose and Dosage Adjustment

- The recommended dose of Adtralza for adult and adolescent patients 12 years and older is an initial dose of 600 mg followed by 300 mg administered every other week as subcutaneous injection.

	Pre-filled Syringe	Pre-filled Pen
Initial Dose	600 mg administered as four 150 mg injections	600 mg administered as two 300 mg injections
Subsequent Maintenance Doses	300 mg administered as two 150 mg injections every other week	300 mg administered as one 300 mg injection every other week

- At prescriber's discretion, every fourth week dosing may be considered for some patients who achieve clear or almost clear skin after 16 weeks of treatment; however, the probability of maintaining clear or almost clear skin may be decreased with dosing every fourth week.
- Some patients with initial partial response may subsequently improve further with continued treatment every other week beyond 16 weeks. At the prescriber's discretion, discontinuation of treatment may be considered in patients who have shown no response after 16 weeks of treatment.

Body weight

For patients with high body weight (>100 kg) who achieve clear or almost clear skin after 16 weeks of treatment, dosage every other week may be more appropriate than every fourth week dosing [see [\(10.3\)](#) CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions].

Elderly patients (≥ 65 years)

No dose adjustment is recommended for elderly patients [see [\(10.3\)](#) CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions].

Hepatic impairment

No dose adjustment is needed in patients with mild hepatic impairment. Very limited data are available in patients with moderate or severe hepatic impairment [see [\(10.3\)](#) CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions].

Renal impairment

No dose adjustment is needed in patients with mild or moderate renal impairment. Very limited data are available in patients with severe renal impairment [see [\(10.3\)](#) CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions].

4.3 Reconstitution

Adtralza does not require reconstitution prior to injection [see [\(6\)](#) DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING].

4.4 Administration

- Adtralza is administered by subcutaneous injection into the thigh or abdomen, except the 5 cm (2 inches) around the navel. If somebody else administers the injection, the upper arm can also be used. Adtralza should not be administered intramuscularly.
- For the initial 600 mg dose, four 150 mg Adtralza pre-filled syringes, or two 300 mg Adtralza pre-filled pens should be administered consecutively in different injection sites within the same body area.
- For each subsequent 300 mg maintenance dose, two 150 mg Adtralza pre-filled syringes, or one 300 mg Adtralza pre-filled pen should be administered. It is recommended to rotate the body area for each subsequent dose.
- Adtralza should not be injected into skin that is tender, damaged or has bruises or scars.

- A patient may self-inject Adtralza or the patient's caregiver may administer Adtralza if their health professional determines that this is appropriate. Proper training should be provided to patients and/or caregivers on the preparation and administration of Adtralza prior to use according to the [PATIENT MEDICATION INFORMATION, INSTRUCTIONS FOR USE](#) section of the product monograph.

4.5 Missed Dose

If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time.

5 OVERDOSAGE

There is no specific treatment for Adtralza overdose.

In clinical studies with tralokinumab, single intravenous doses of up to 30 mg/kg and multiple subcutaneous doses of 600 mg every 2 weeks for 12 weeks were found to be well tolerated.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 1-1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/Strength/Composition	Non-medicinal Ingredients
Subcutaneous Injection	Each single-use pre-filled syringe contains 150 mg of tralokinumab in 1 mL solution (150 mg/mL). The pre-filled syringe is composed of Type-1 clear glass with a fixed 27 gauge, ½ inch, 5 bevel needle and a needle guard.	Acetic acid Polysorbate 80 Sodium acetate trihydrate Sodium chloride Water for injection
	Each single-use pre-filled pen contains 300 mg of tralokinumab in 2 mL solution (150 mg/mL). The pre-filled pen is composed of Type-1 clear glass with a fixed 27 gauge, ½ inch, 5 bevel needle and a needle guard.	

Adtralza is supplied as a preservative-free, clear to opalescent, colourless to pale yellow solution.

Adtralza is available in the following pack sizes:

Pre-filled syringe (150 mg)

- 1 carton containing 2 pre-filled syringes
- 1 multipack carton containing 4 pre-filled syringes (2 packs of 2)

Not all pack sizes may be marketed.

None of the components of the pre-filled syringe or the needle cover are made with natural rubber latex (NRL), dry natural rubber (DNR), or any derivatives (of NRL or DNR).

Pre-filled pen (300 mg)

- 1 carton containing 2 pre-filled pens
- 1 multipack carton containing 6 pre-filled pens (3 packs of 2)

Not all pack sizes may be marketed.

None of the components of the pre-filled pen are made with natural rubber latex (NRL), dry natural rubber (DNR), or any derivatives (of NRL or DNR).

7 WARNINGS AND PRECAUTIONS

Immune

Hypersensitivity

Hypersensitivity reactions have been reported following the use of Adtralza. If a systemic hypersensitivity reaction (immediate or delayed) occurs, administration of Adtralza should be discontinued immediately and appropriate therapy initiated.

Anaphylactic reaction has been reported very rarely in clinical studies following administration of tralokinumab.

Helminth infection

Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if Adtralza will influence the immune response against helminth infections by inhibiting IL-13 signaling.

Treat patients with pre-existing helminth infections before initiating Adtralza. If patients become infected while receiving Adtralza and do not respond to anti-helminth treatment, treatment with Adtralza should be discontinued until infection resolves.

Conjunctivitis

Conjunctivitis occurred more frequently in subjects with atopic dermatitis who received Adtralza than in subjects who received placebo. Advise patients to report new onset or worsening eye symptoms to their healthcare professional. Patients treated with Adtralza who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination, as appropriate [see (8) ADVERSE REACTIONS].

7.1 Special Populations

7.1.1 Pregnant Women

No studies have been conducted with Adtralza in pregnant women and relevant data from clinical use are very limited.

As a precautionary measure, it is preferable to avoid the use of Adtralza during pregnancy.

Human IgG antibodies are known to cross the placental barrier; therefore, Adtralza may be transmitted from the mother to the developing fetus. In a developmental toxicity study conducted in cynomolgus monkeys, tralokinumab was detected in monkey infant serum following *in utero* exposure, indicating transport across the placenta [see (16) NON-CLINICAL TOXICOLOGY].

7.1.2 Breast-feeding

It is unknown whether Adtralza is excreted in human milk or absorbed systemically after ingestion. A decision must be made whether to discontinue breast-feeding or to discontinue Adtralza therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

7.1.3 Pediatrics

Health Canada has not authorized an indication for pediatric use in patients < 12 years of age as no data are available for this age group [see [\(1.1\)](#) INDICATIONS, Pediatrics].

7.1.4 Geriatrics

Evidence from 77 patients \geq 65 years of age that were exposed to Adtralza in 5 atopic dermatitis clinical studies suggests that use in the geriatric population is not associated with differences in safety or efficacy [see [\(1.2\)](#) INDICATIONS, Geriatrics].

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adults

The most frequently (\geq 10%) reported adverse drug reactions (ADRs) in the pool of 5 studies were upper respiratory tract infections (23%) compared with 17% in the placebo group. The majority of these were reported as common cold. All of the reactions were mild or moderate in severity.

The proportion of patients who discontinued treatment due to adverse events was 2.3% in the Adtralza group and 2.8% in the placebo group during the initial treatment period of up to 16 weeks.

During the maintenance treatment period of the monotherapy studies (ECZTRA 1 and ECZTRA 2) from 16 to 52 weeks, upper respiratory tract infections were reported at an exposure-adjusted rate of 64 per 100 patient-years for Adtralza 300 mg every 2 weeks (Q2W) and Adtralza 300 mg every 4 weeks (Q4W) compared to 94 per 100 patient-years for Adtralza 300 mg Q2W in the initial treatment period. In the continuation treatment period of ECZTRA 3 (up to 32 weeks), the exposure-adjusted rate was 98 per 100 patient-years for Adtralza 300 mg Q2W + topical corticosteroids (TCS) and 63 per 100 patient-years for Adtralza 300 mg Q4W + TCS compared to 120 per 100 patient-years for Adtralza 300 mg Q2W + TCS in the initial treatment period.

Across all treatment periods (up to 52 weeks), the majority (>80%) of the upper respiratory tract infections were classified as mild and non-serious.

Adolescents

The safety profile of Adtralza in adolescent patients 12 years and older, followed through the initial treatment period of 16 weeks and the long-term period of 52 weeks, was similar to the safety profile observed in adults.

Open-Label Extension Study in Adults and Adolescents

The long-term safety of Adtralza is further assessed in an open-label extension study (ECZTEND) for up to 5 years of treatment in adults and adolescents with moderate-to-severe atopic dermatitis, who have previously participated in tralokinumab clinical trials, receiving 300 mg of tralokinumab every two weeks (Q2W). The long-term safety profile based on interim safety data is overall consistent with the safety profile observed up to week 16 in the pool of the 5 adult studies.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adults

The safety of Adtralza was evaluated based on a pool of 5 randomized, double-blind, placebo-controlled studies in patients with moderate-to-severe atopic dermatitis including three phase 3 studies (ECZTRA 1, ECZTRA 2, and ECZTRA 3), a dose-ranging study and a vaccine-response study. The safety population had a mean age of 38 years; 43% of patients were female, 67% were white, 20% were Asian, and 10% were black; in terms of co-morbid conditions, 38% of the patients had asthma, 47% had hay fever, 34% had food allergy, and 20% had allergic conjunctivitis.

In these 5 atopic dermatitis studies, 1991 patients were treated with subcutaneous injections of Adtralza, with or without concomitant topical corticosteroids (TCS). A total of 807 patients were treated with Adtralza for at least 1 year.

The long-term safety of Adtralza was assessed in 2 monotherapy studies up to 52 weeks and in a combination study with TCS up to 32 weeks. The safety profile at 39 months in the long-term extension study (ECZTEND) was overall consistent with the safety profile observed up to week 16 in previous studies.

Table 1-2 summarizes the adverse reactions occurring in the atopic dermatitis clinical trials at a rate of $\geq 1\%$ in the Adtralza 300 mg every other week monotherapy group (ECZTRA 1 and ECZTRA 2), and in the Adtralza 300 mg every other week + TCS study (ECZTRA 3).

Table 1-2: List of adverse reactions occurring with a frequency of $\geq 1\%$ in ECZTRA 1, ECZTRA 2 and ECZTRA 3 clinical trials through week 16

System organ class ADR	Monotherapy ^a (up to 16 weeks)		Adtralza + TCS ^b (up to 16 weeks)	
	Adtralza (N=1194; PYE=354.46)	Placebo (N=396; PYE=114.47)	Adtralza + TCS (N=252; PYE=75.03)	Placebo + TCS (N=126; PYE=37.94)
	N (%)	N (%)	N (%)	N (%)
Blood and lymphatic system disorders				
Eosinophilia	17 (1.4)	2 (0.5)	3 (1.2)	0 (0.0)
Eye disorders				
Conjunctivitis allergic (PT)	28 (2.3)	5 (1.3)	5 (2.0)	2 (1.6)
General disorders and administration site conditions				
Injection site reactions (HLT) (i.e., redness, swelling)	87 (7.3)	16 (4.0)	27 (10.7)	1 (0.8)
Infections and infestations				
Upper respiratory tract infections ^c	284 (23.8)	80 (20.2)	73 (29.0)	19 (15.1)
Conjunctivitis (PT)	61 (5.1)	7 (1.8)	28 (11.1)	4 (3.2)

Abbreviations:

ADR = adverse drug reaction; HLT = high-level term; N = number of patients (with events); PT = preferred term; PYE = patient-years of exposure; TCS = topical corticosteroids

^a Pooled analysis of ECZTRA 1 and 2.

^b Analysis of ECZTRA 3 where subjects were on background TCS treatment.

^c Upper respiratory tract infections cluster includes upper respiratory tract infection, viral upper respiratory tract infection, pharyngitis, and nasopharyngitis; mainly reported as common cold.

Conjunctivitis

Conjunctivitis occurred more frequently in atopic dermatitis patients who received Adtralza (5.4%) compared to placebo (1.9%) in the initial treatment period of up to 16 weeks in the pool of 5 studies. Most patients recovered or were recovering during the treatment period.

Infections

In the pool of 5 studies in atopic dermatitis, serious infections were reported in 0.4% of patients treated with Adtralza and 1.1% of patients treated with placebo during the initial treatment period of up to 16 weeks.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity with Adtralza.

No immunogenicity related adverse events such as immune-complex disease, serum sickness/serum sickness-like reactions, or anaphylaxis were observed in 1991 patients treated with Adtralza in the pool of 5 studies in atopic dermatitis.

Anti-Drug-Antibody (ADA) responses were not associated with any impact on Adtralza exposure, safety, or efficacy.

In ECZTRA 1, ECZTRA 2, ECZTRA 3, and the vaccine-response study (ECZTRA 5), the incidence of ADA up to 16 weeks was 1.4% for patients treated with Adtralza and 1.3% for patients treated with placebo; neutralizing antibodies were seen in 0.1% of patients treated with Adtralza and 0.2% of patients treated with placebo.

The ADA incidence for patients who received Adtralza up to 52 weeks was 4.4%; 0.7% had persistent ADA and 0.9% had neutralizing antibodies.

The observed incidence of persistent ADA responses and neutralizing activity in the assay are highly dependent on the sensitivity and specificity of the assay used. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease status of the individual patient. For these reasons, comparison of the incidence of antibodies to Adtralza with the incidence of antibodies to other products may be misleading.

8.2.1 Clinical Trial Adverse Reactions – Adolescents

The safety of Adtralza was assessed in patients 12 to 17 years of age (adolescents) with moderate-to-severe atopic dermatitis in a monotherapy study of 289 adolescents (ECZTRA 6) and in a long-term open label extension study (ECZTEND) including 127 adolescents transferred from ECZTRA 6. The safety profile of Adtralza in these adolescent patients, followed through the initial treatment period of 16 weeks and the long-term treatment period of 52 weeks (ECZTRA 6), as well as in the interim safety data from the long-term open-label extension study up to 21 months (ECZTEND) was similar to the safety profile from studies in adults.

In the adolescent trial, conjunctivitis occurred in 1.0% of atopic dermatitis patients treated with Adtralza and in no patients treated with placebo in the initial treatment period of 16 weeks. Conjunctivitis allergic occurred at similar frequency in atopic dermatitis adolescent patients, who received Adtralza (2.1%) compared to placebo (2.1%) in the initial treatment period of 16 weeks.

8.3 Less Common Clinical Trial Adverse Reactions (< 1%)

Eye disorders: Keratitis

8.3.1 Less Common Clinical Trial Adverse Reactions (< 1%) – Adolescents

None

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Eosinophilia was reported in 1.3% of patients treated with Adtralza and 0.3% of patients treated with placebo during the initial treatment period of up to 16 weeks in the pool of 5 studies in adults. Adtralza-treated patients had a greater mean initial increase from baseline in eosinophil count compared to patients treated with placebo. However, the increase in eosinophil count of the Adtralza-treated patients was transient, and mean eosinophil counts returned to baseline during continued treatment. The safety profile for patients with eosinophilia was comparable to the safety profile for all patients.

8.5 Post-Market Adverse Reactions

Not applicable, as post-market adverse reactions have yet to be reported.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Interactions with cytochrome P450

Tralokinumab is not expected to undergo metabolism by hepatic enzymes or renal elimination. There is limited effect of tralokinumab on the metabolism of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 substrates. Therefore, an impact of tralokinumab on the pharmacokinetics of concomitant medicines metabolized by the CYP enzymes is unlikely [see [\(9.4\)](#) Drug-Drug Interactions].

9.3 Drug-Behavioural Interactions

Drug-behavioural interactions have not been established.

9.4 Drug-Drug Interactions

Drug-Drug Interactions

In a clinical trial of 18-20 evaluable subjects with atopic dermatitis, the effects of repeated administration of tralokinumab injection on the pharmacokinetics of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), metoprolol (CYP2D6 substrate) and midazolam (CYP3A4 substrate) were evaluated. The C_{max} of midazolam at Week 15 decreased by 22%, after tralokinumab administration. The AUC and C_{max} of other CYP substrates investigated were comparable before and after tralokinumab administration.

Drug-Vaccine Interactions

Live Vaccines:

Adtralza has not been studied with live vaccines. Live vaccines should not be given concurrently with Adtralza.

Non-Live Vaccines:

Immune responses to non-live vaccines were assessed in a study in which adult patients with atopic dermatitis were treated with an initial dose of 600 mg (four 150 mg injections) followed by 300 mg every second (other) week administered as subcutaneous injection. After 12 weeks of Adtralza administration, patients were vaccinated with a combined tetanus, diphtheria, and acellular pertussis vaccine, and a meningococcal vaccine and immune responses were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal vaccine were similar in Adtralza-treated and placebo-treated patients.

No adverse interactions between either of the non-live vaccines or Adtralza were noted in the study. Therefore, patients receiving Adtralza may receive concurrent inactivated or non-live vaccinations.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Tralokinumab is a fully human IgG4 monoclonal antibody that specifically binds to the type 2 cytokine interleukin-13 (IL-13) and inhibits its interaction with the IL-13 receptors, IL-13R α 1 and IL-13R α 2. Tralokinumab neutralizes the activity of IL-13 by blocking its interaction with the IL-13R α 1/IL-4R α receptor complex.

IL-13 is a major driver of type 2 inflammation in atopic dermatitis, with atopic dermatitis skin showing overexpression of IL-13. IL-13 signals via the IL-13R α 1/IL-4R α receptor complex and stimulates inflammatory responses, contributes to itch induction, and impairs the expression of proteins necessary for a normal skin barrier.

10.2 Pharmacodynamics

In clinical studies, treatment with tralokinumab was associated with decreases from baseline in concentrations of Th2 and Th22 immunity biomarkers in the blood, such as thymus and activation-regulated chemokine (TARC/CCL17), periostin, IL-22, LDH and serum IgE. Decreases from baseline in serum concentrations of CCL17, IL-22 and IgE were also observed in adolescent patients, however, CCL17 and IL-22 concentrations were reduced to a lesser extent than in adults. Furthermore, tralokinumab treatment resulted in reduced epidermal

thickness and decreased expression of Keratin 16 and Ki-67 in AD skin. The protein expression of loricrin was upregulated in AD skin, further indicating that the skin barrier was improved with tralokinumab. Finally, tralokinumab suppressed expression of genes in the Th2 pathway, including CCL17, CCL18 and CCL26 as well as markers of Th17- and Th22-regulated genes in lesional skin. In addition, patients treated with tralokinumab achieved a more than 10-fold higher reduction in abundance of *Staphylococcus aureus* at week 16 compared to placebo. Similar results on *Staphylococcus aureus* reductions were observed in adolescents. In these patients, treatment with Adtralza resulted in a shift of the stratum corneum lipid profile from a lesional to that of non-lesional skin.

10.3 Pharmacokinetics

Exposure of tralokinumab increases proportionally to the dose of tralokinumab over a range of investigated doses 0.1-10 mg/kg in adult patients.

Table 1-3: Summary of tralokinumab pharmacokinetic parameters in subjects with atopic dermatitis

Dose Regimen ^a	C _{max,ss} (mcg/mL)	AUC _{t,ss} (mcg x day/mL)	t _{max} (day)	V _d (L)	t _{1/2} (day)	CL (L/day)
Adults • 300 mg Q2W	118.4 ^b	1583 ^c	5-8 ^d	4.2 ^e	22 ^e	0.149 ^e
Adolescents • 300 mg Q2W	141.7 ^f	1842 ^f	5-8 ^d	3.4 ^g	22	0.121 ^g

SS=At steady state

^a Adult data are based on observed data; Adolescent data are based on simulated data

^b Mean of observed data at week 15 from ECZTRA 1, one week after the latest dose

^c Mean AUC_{0-tau} at steady state based on observed data from ECZTRA 1

^d Estimated by population PK analysis and range of t_{max} across phase 1 trials

^e Estimated by population PK analysis

^f Simulated by population PK analysis based on a median body weight of 59 kg for adolescents (ECZTRA 6)

^g V_d and CL are dependent on body weight; the values are shown for a 59 kg adolescent subject

Absorption: After subcutaneous (SC) dose of tralokinumab median times to maximum concentration in serum (t_{max}) were 5-8 days. The absolute bioavailability of tralokinumab following SC dosing is 76%.

Steady-state concentrations were achieved by week 16 following a 600 mg starting dose and 300 mg every other week in adult and adolescent subjects. Across adult clinical studies (ECZTRA 1, ECZTRA 2 and ECZTRA 3), the mean ±SD steady-state trough concentration ranged from 98.0±41.1 mcg/mL to 101.4±42.7 mcg/mL for a 300 mg dose administered every other week. For adolescent patients 12 to 17 years of age with atopic dermatitis, the mean ±SD steady-state trough concentration (at week 16) was 112.8±39.23 mcg/mL for a 300 mg dose administered every other week.

Distribution: A volume of distribution for tralokinumab of approximately 4.2 L was estimated by population PK analysis.

Metabolism: Specific metabolism studies were not conducted because tralokinumab is a protein. Tralokinumab is expected to degrade to small peptides and individual amino acids.

Elimination: Tralokinumab is eliminated through a non-saturable proteolytic pathway. Half-life is 22 days, consistent with the typical estimate for human IgG4 monoclonal antibodies targeting soluble cytokines.

Special Populations and Conditions

- **Pediatrics:** The pharmacokinetics of tralokinumab in pediatric patients below 12 years of age has not been studied.
- **Geriatrics:** Age was not found to be associated with clinically relevant impact of systemic exposure of tralokinumab determined by population PK analysis. 131 subjects ≥ 65 years were included in the analysis.
- **Sex:** Gender was not found to be associated with any clinically meaningful impact on the systemic exposure of tralokinumab determined by population PK analysis.
- **Ethnic Origin:** Race was not found to be associated with any clinically meaningful impact on the systemic exposure of tralokinumab by population PK analysis.
- **Hepatic Insufficiency:** Tralokinumab, as a monoclonal antibody, is not expected to undergo significant hepatic elimination. No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of tralokinumab. Mild hepatic impairment was not found to affect the PK of tralokinumab determined by population PK analysis. Moderate or severe hepatic impairment was not found to affect the PK of tralokinumab. Very limited data are available in patients with moderate or severe hepatic impairment.
- **Renal Insufficiency:** Tralokinumab, as a monoclonal antibody, is not expected to undergo significant renal elimination. No clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of tralokinumab. Population PK analysis did not identify mild or moderate renal impairment as having a clinically meaningful influence on the systemic exposure of tralokinumab. Very limited data are available in patients with severe renal impairment.
- **Body Weight:** Tralokinumab trough concentrations were lower in patients with higher body weight.

11 STORAGE, STABILITY AND DISPOSAL

Store in a refrigerator (2-8°C). Do not freeze.

Store in the original carton in order to protect from light. The pre-filled syringe or pre-filled pen should not be exposed to heat or direct sunlight and should not be shaken.

If necessary, pre-filled syringes or pre-filled pens may be kept at room temperature up to 30°C for a maximum of 14 days, within the expiration date period of the product. Do not store above 30°C.

If the carton needs to be removed permanently from the refrigerator, the date of removal may be recorded on the outer carton. Discard the product if it is not used within 14 days of storage at room temperature.

After removing the pre-filled syringe or pre-filled pen from the refrigerator, it should be allowed to reach room temperature by waiting for 30 minutes before injecting the pre-filled syringe, or 45 minutes before injecting the pre-filled pen.

Do not put the pre-filled syringes or pre-filled pens back in the refrigerator once they have reached room temperature.

The solution should be clear to opalescent, colourless to pale yellow. If the solution is cloudy, discoloured or contains visible particulate matter, the solution should not be used. Do not use if the pre-filled syringe or pre-filled pen is damaged or has been dropped on a hard surface.

Adtralza is sterile and does not contain preservatives; therefore, discard any unused product remaining in the pre-filled syringe or pre-filled pen.

After injection, safely dispose of the used pre-filled syringes or pre-filled pens in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

For special handling instructions on how to properly dispose of Adtralza following an injection, refer to the [PATIENT MEDICATION INFORMATION, INSTRUCTIONS FOR USE](#) section of the product monograph.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Tralokinumab
Chemical name:	Not applicable. Tralokinumab is an immunoglobulin.
Molecular formula:	$C_{6374}H_{9822}N_{1698}O_{2014}S_{44}$
Molecular mass:	Approximately 147 kDa (including oligosaccharides)
Structural formula:	The antibody is composed of two heavy chains, and two light chains covalently linked with four inter-chain disulfide bonds. Tralokinumab has an N-linked oligosaccharide attachment site. The oligosaccharides are predominantly fucosylated biantennary complex-type oligosaccharides.
Physicochemical properties:	Tralokinumab is supplied as a sterile, preservative-free solution for subcutaneous administration. The solution is colourless to pale yellow and clear to opalescent, with pH of 5.5.

Product Characteristics:

Tralokinumab is produced in mouse myeloma cells by recombinant DNA technology. No materials of human origin are used in the manufacture of Adtralza. The cell cultivation and harvest process consists of five steps. Following the final harvest step, the clarified conditioned medium containing tralokinumab is further processed through a series of purification steps. Purification involves chromatography steps to remove product- and process-related impurities, and dedicated virus clearance steps. A concentration and diafiltration step, followed by a formulation step and a 0.2 micron filtration step, are then used to generate the final drug substance.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Atopic Dermatitis in Adults

The efficacy and safety of Adtralza (tralokinumab injection) as monotherapy and with concomitant topical corticosteroids were evaluated in three pivotal randomized, double-blind, placebo-controlled studies (ECZTRA 1, ECZTRA 2 and ECZTRA 3) in 1976 patients 18 years of age and older with moderate-to-severe atopic dermatitis (AD) who had a previous inadequate response to topical medication. Disease severity was defined by Investigator's Global Assessment (IGA) score of 3 or 4 (moderate or severe), an Eczema Area and Severity Index (EASI) score of ≥ 16 at baseline, and a minimum body surface area (BSA) involvement of $\geq 10\%$.

In all three studies (Table 2-1), patients received 1) an initial dose of 600 mg Adtralza (four 150 mg injections) on day 1, followed by 300 mg every two weeks (Q2W) up to week 16, or 2) matching placebo. In ECZTRA 3, patients received concomitant topical corticosteroids (i.e., 0.1% mometasone furoate) on active lesions as needed. Adtralza was administered by subcutaneous (SC) injection in all studies.

In ECZTRA 1 and ECZTRA 2, to evaluate the maintenance of response, patients responding to initial 16-week treatment with Adtralza (i.e., IGA 0 or 1, or EASI-75) were re-randomized to 1) Adtralza 300 mg Q2W, or 2) Adtralza 300 mg Q4W (alternating Adtralza 300 mg and placebo Q2W), or 3) placebo Q2W up to 52 weeks. Patients responding to the initial 16-week treatment with placebo continued on placebo. Patients not achieving IGA 0 or 1 or EASI-75 at week 16 and patients who did not maintain the response during the maintenance period were transferred to open-label treatment with Adtralza 300 mg Q2W with optional use of topical corticosteroids (TCS).

In ECZTRA 3, patients responding to the initial 16-week treatment with Adtralza + TCS were re-randomized to 1) Adtralza 300 mg Q2W + TCS, or 2) Adtralza 300 mg Q4W + TCS (alternating placebo 300 mg Q2W + TCS) up to 32 weeks. Patients responding to the initial 16-week treatment with placebo + TCS continued on placebo + TCS. Patients, who at week 16 did not achieve IGA 0 or 1 or EASI-75, continued on Adtralza 300 mg Q2W + TCS treatment, irrespectively of their initial treatment.

In all three pivotal studies, the primary endpoints were achievement of IGA 0 or 1 and EASI-75 from baseline to week 16. Secondary endpoints included the reduction of itch as defined by at least 4-point improvement in the Worst Daily Pruritus Numeric Rating Scale (NRS), reduction in the SCORing Atopic Dermatitis (SCORAD) scale, change in Dermatology Life Quality Index (DLQI), and a reduction of at least 50% and 90% in EASI (EASI-50 and EASI-90) from baseline to week 16.

Table 2-1: Summary of patient demographics for clinical trials in moderate-to-severe atopic dermatitis in adults

Study #	Trial design	Dosage, route of administration and duration	Study patients (n)	Mean age (SD)	Sex
ECZTRA 1	Phase 3 randomized, double-blind, placebo-controlled, monotherapy, efficacy and safety	300 mg Adtralza subcutaneous injection (two 150 mg injections), up to 52 weeks	Adult patients with moderate-to-severe AD (n=802)	38.8 (14.1)	M=474 (59.1%) F=328 (40.9%)
ECZTRA 2	Phase 3 randomized, double-blind, placebo-controlled, monotherapy, efficacy and safety	300 mg Adtralza subcutaneous injection (two 150 mg injections), up to 52 weeks	Adult patients with moderate-to-severe AD (n=794)	36.7 (14.6)	M=473 (59.6%) F=321 (40.4%)
ECZTRA 3	Phase 3 randomized, double-blind, placebo-controlled, combination with TCS, efficacy and safety	300 mg Adtralza subcutaneous injection (two 150 mg injections), up to 32 weeks	Adult patients with moderate-to-severe AD (n=380)	39.1 (15.2)	M=209 (55.0%) F=171 (45.0%)

Atopic Dermatitis in Adolescents

The efficacy and safety of Adtralza monotherapy in adolescent patients was evaluated in a multicentre, randomized, double-blind, placebo-controlled study (ECZTRA 6) in 289 adolescent patients 12 to 17 years of age with moderate-to-severe atopic dermatitis defined by IGA score ≥ 3 in the overall assessment of AD lesions on a severity scale of 0 to 4, an EASI score ≥ 16 at baseline, and a minimum BSA involvement of $\geq 10\%$. Eligible patients enrolled into this study had previous inadequate response to topical medication.

Patients received an initial dose of 600 mg Adtralza or 300 mg on day 1 followed by 300 mg Q2W or 150 mg Q2W, respectively, up to week 16. To evaluate the maintenance of response up to week 52, patients responding (i.e., achieved IGA 0 or 1, or EASI-75) to the initial 16-week treatment with Adtralza 150 mg Q2W or 300 mg Q2W without the use of rescue medication were re-randomized to Q2W or Q4W (subjects initially treated with Adtralza 300 mg were re-randomized 1:1 to Adtralza 300 mg Q2W or Adtralza 300 mg Q4W; subjects initially treated with Adtralza 150 mg were re-randomized 1:1 to Adtralza 150 mg Q2W or Adtralza 150 mg Q4W).

Patients not achieving IGA 0 or 1, or EASI-75 at week 16, and patients who did not maintain the response during the maintenance treatment period, and those that used rescue medication during the initial period, were transferred to open-label treatment with Adtralza 300 mg Q2W

with optional use of topical corticosteroids. Patients randomized to placebo in the initial treatment period who achieved a clinical response at week 16 continued to receive placebo Q2W in the maintenance treatment period.

The primary endpoints were the proportion of patients with IGA 0 or 1 at week 16 and the proportion of patients with EASI-75 at week 16. Secondary endpoints included the reduction in itch, as measured by the proportion of subjects with ≥ 4 -point improvement in Adolescent Worst Pruritus NRS from baseline, the absolute change in SCORAD from baseline to week 16 and the absolute change in CDLQI from baseline to week 16.

Table 2-2: Summary of patient demographics in moderate-to-severe atopic dermatitis in adolescents

Study #	Trial design	Dosage, route of administration and duration	Study patients (n)	Mean age (SD)	Sex
ECZTRA 6	Phase 3 randomized, double-blind, placebo-controlled, monotherapy, efficacy and safety	150 mg or 300 mg Adtralza subcutaneous injection (one 150 mg injection or two 150 mg injections), up to 52 weeks	Adolescent patients with moderate-to-severe AD (n=289)	14.6 (1.7)	M=149 (51.6%) F=140 (48.4%)

14.2 Study Results

Atopic Dermatitis in Adults

Baseline characteristics

In the monotherapy studies (ECZTRA 1 and ECZTRA 2), across all treatment groups, the mean age was 37.8, the mean weight was 76.0 kg, 40.7% were female, 66.5% were white, 22.9% were Asian, and 7.5% were black. In these studies, 49.9% of patients had a baseline IGA score of 3 (moderate AD), 49.7% of patients had a baseline IGA of 4 (severe AD), the mean baseline EASI score was 32.3, the mean baseline Worst Daily Pruritus NRS was 7.8, the mean baseline DLQI was 17.3, the baseline mean SCORAD score was 70.4, 63.3% of patients had received prior systemic steroids, and 42.5% of patients had received prior other systemic immunosuppressants (cyclosporine, methotrexate, azathioprine and mycophenolate).

In the concomitant TCS study (ECZTRA 3), across both treatment groups, the mean age was 39.1 years, the mean weight was 79.4 kg, 45.0% were female, 75.8% were white, 10.8% were Asian, and 9.2% were black. In this study, 53.2% of patients had a baseline IGA score of 3, 46.3% of patients had a baseline IGA of 4, the mean baseline EASI score was 29.4, the baseline Worst Daily Pruritus NRS was 7.7, the baseline mean DLQI was 17.5, the baseline mean SCORAD score was 67.6, and 39.2% of patients received prior systemic immunosuppressants.

Clinical response

Monotherapy Studies (ECZTRA 1 and ECZTRA 2) and Concomitant TCS Study (ECZTRA 3) - Initial Treatment Period (Weeks 0-16)

The efficacy results of the pivotal Phase III trials are included in Table 2-3 below.

Table 2-3: Efficacy results of Adtralza at week 16 in ECZTRA 1 (monotherapy), ECZTRA 2 (monotherapy) and ECZTRA 3 (combination therapy with TCS) (FAS)

Monotherapy						
	ECZTRA 1		ECZTRA 2		ECZTRA 3	
	Week 16		Week 16		Week 16	
	Placebo	Adtralza 300 mg Q2W	Placebo	Adtralza 300 mg Q2W	Placebo + TCS	Adtralza 300 mg Q2W + TCS
Number of patients randomized and dosed (FAS)	197	601	201	591	126	252
IGA 0 or 1, % responders ^{a,b)}	7.1	15.8*	10.9	22.2*	26.2	38.9*
EASI-50, % responders ^{a)}	21.3	41.6*	20.4	49.9*	57.9	79.4*
EASI-75, % responders ^{a)}	12.7	25.0*	11.4	33.2*	35.7	56.0*
EASI-90, % responders ^{a)}	4.1	14.5*	5.5	18.3*	21.4	32.9*
Pruritus NRS (\geq 4-point improvement, % responders) ^{a,c)}	10.3 (20/194)	20.0* (119/594)	9.5 (19/200)	25.0* (144/575)	34.1 (43/126)	45.4* (113/249)

LS=Least squares; SE=Standard error; FAS: Full Analysis Set - includes all patients randomized and dosed. IGA=Investigator's Global Assessment; EASI=Eczema Area and Severity Index; NRS=Numeric Rating Scale. If needed to control intolerable symptoms of atopic dermatitis, patients were permitted to receive rescue treatment at the discretion of the investigator.

a) Patients who received rescue treatment or had missing data were considered non-responders in the analyses.

b) Responder was defined as a patient with IGA 0 or 1 ("clear" or "almost clear" on a 0-4 IGA scale).

c) The percentage is calculated relative to the number of patients with a baseline value > 4.

* $p < 0.05$

A numerically greater improvement in Worst Daily Pruritus NRS (mean percent change from baseline) in patients randomized to Adtralza compared to placebo was observed as early as week 1 for ECZTRA 1 and ECZTRA 2 and week 2 for ECZTRA 3 and was maintained at each visit throughout the 16-week period. The improvement in Worst Daily Pruritus NRS occurred in conjunction with the improvement of DLQI and objective signs of atopic dermatitis including SCORAD.

In ECZTRA 3, patients who received Adtralza 300 mg Q2W from week 0 to 16 used 50% less of the supplied TCS at week 16 as compared to patients who received placebo.

Monotherapy Studies (ECZTRA 1 and ECZTRA 2) – Maintenance Period (Weeks 16-52)

In an analysis of the maintenance period (Weeks 16-52), the findings from the Q2W dosage regimen indicate that the treatment benefit based on both IGA 0 or 1 and EASI-75 was maintained.

Additionally, in patients who switched from Q2W to Q4W dosing at Week 16, a favourable trend was observed on both IGA 0 or 1 and EASI-75 at Week 52; however, the magnitude of effect was numerically less than that observed with the Q2W dosage regimen.

32-Week Concomitant TCS Study (ECZTRA 3) - Maintenance Period (Weeks 16-32)

In an analysis of the maintenance period (Weeks 16-32), the findings from the Q2W dosage regimen indicate that the treatment benefit based on both IGA 0 or 1 and EASI-75 was maintained.

Additionally, in patients who switched from Q2W to Q4W dosing at Week 16, a favourable trend was observed on both IGA 0 or 1 and EASI-75 at Week 32; however, the magnitude of effect was numerically less than that observed with the Q2W dosage regimen.

Quality of Life/Patient-Reported Outcomes

In both monotherapy studies (ECZTRA 1 and ECZTRA 2) and in the TCS combination study (ECZTRA 3), improvements in patient reported outcomes were associated with Adtralza 300 mg Q2W.

A larger proportion of subjects treated with Adtralza had an improvement in eczema-related sleep NRS score, SF-36 (mental and physical components), and a ≥ 4 -points improvement (corresponding to minimal clinically important difference) in Patient-Oriented Eczema Measure (POEM) and DLQI in ECZTRA 1, ECZTRA 2, and ECZTRA 3 studies compared to placebo.

In ECZTRA 1, the proportion of Adtralza-treated responders for POEM and DLQI was 43.0% and 44.6%, respectively, compared to 18.0% and 31.6% for placebo at week 16.

In ECZTRA 2, the proportion of Adtralza-treated responders for POEM and DLQI was 54.4% and 56.3%, respectively, compared 22.1% and 27.3% for placebo at week 16.

In ECZTRA 3, the proportion of Adtralza-treated responders for POEM and DLQI was 78.4% and 83.5%, respectively, compared to 59.3% and 65.9% for placebo at week 16.

Atopic Dermatitis in Adolescents

Baseline characteristics

In ECZTRA 6, the mean age was 14.6 years, the mean weight was 61.5 kg, 48.4% were female, 56.7% were White, 24.6% were Asian, and 11.1% were Black. At baseline 53.3% of patients had a baseline IGA score of 3 (moderate AD), 46.7% of patients had a baseline IGA of 4 (severe AD), the mean BSA involvement was 51.1%, and 21.1% of patients had received prior systemic immunosuppressants (cyclosporine, methotrexate, azathioprine and mycophenolate). Also, at baseline the mean EASI score was 31.7, the baseline Adolescent Worst Pruritus NRS score was 7.6, the baseline mean SCORAD score was 67.8, the baseline mean POEM score was 20.4, and the baseline mean Children Dermatology Life Quality Index (CDLQI) was 13.2.

Clinical response

Monotherapy Study (ECZTRA 6) - Initial Treatment Period (Weeks 0-16)

The efficacy results at week 16 for adolescent patients are presented in Table 2-4.

Table 2-4: Efficacy results of Adtralza at week 16 in ECZTRA 6 (monotherapy) in Adolescents (FAS)

	ECZTRA 6	
	Week 16	
	Placebo	Adtralza 300 mg Q2W
Number of patients randomized and dosed (FAS)	94	97
IGA 0 or 1, % responders ^{a,b)}	4.3	17.5*
EASI-50, % responders ^{a)}	13.8	51.5*
EASI-75, % responders ^{a)}	6.4	27.8*
EASI-90, % responders ^{a)}	4.3	17.5*
Pruritus NRS (≥ 4 -point improvement, % responders) ^{a,c)}	3.3 (3/90)	25.0* (24/96)

LS=Least squares; SE=Standard error; FAS: Full Analysis Set - includes all patients randomized and dosed. IGA=Investigator's Global Assessment; EASI=Eczema Area and Severity Index; NRS=Numeric Rating Scale. If needed to control intolerable symptoms of atopic dermatitis, patients were permitted to receive rescue treatment at the discretion of the investigator.

a) Patients who received rescue treatment from week 2 to week 16 or had missing data were considered non-responders.

b) Responder was defined as a patient with IGA 0 or 1 ("clear" or "almost clear" on a 0-4 IGA scale).

c) The percentage is calculated relative to the number of subjects with a baseline value ≥ 4 .

* $p < 0.05$

* $p < 0.05$ (not controlled for type I error)

A numerically greater improvement in Worst Daily Pruritus NRS (mean percent change from baseline) in patients randomized to Adtralza compared to placebo was observed at week 16 in ECZTRA 6. The improvement in Worst Daily Pruritus NRS occurred in conjunction with the improvement of CDLQI and objective signs of atopic dermatitis including SCORAD.

Monotherapy Study (ECZTRA 6) – Maintenance Period (Weeks 16-52)

In an exploratory analysis of the maintenance period (Weeks 16-52), the findings from the Q2W and Q4W dosage regimens indicate that the treatment benefit based on IGA 0 or 1 and EASI-75 was maintained.

Quality of Life/Patient-Reported Outcomes

Greater improvements in patient-reported symptoms and impacts on quality of life (e.g., sleep, itch) were observed at week 16 in the Adtralza 300 mg group compared with placebo, as measured by the proportion of patients with ≥ 6 -point improvement (corresponding to minimal clinically important difference) in POEM and the proportion of patients with ≥ 6 -point improvement in CDLQI.

The proportion of Adtralza-treated responders for POEM and CDLQI for the 300 mg group was 46.8% and 39.5%, respectively, compared to 10.5% and 15.9% for placebo at week 16.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: In a 26-week repeat-dose toxicity study in cynomolgus monkeys, tralokinumab was well tolerated at weekly intravenous doses of 10, 30, and 100 mg/kg body weight. There were no tralokinumab-related adverse effects observed, including on cardiovascular function. At the no observed-adverse-effect level (NOAEL) of 100 mg/kg body weight, the systemic exposure was approximately 36-fold higher than atopic dermatitis adult patients receiving 300 mg of Adtralza Q2W and 31-fold higher than adolescent patients receiving 300 mg of Adtralza Q2W, based on AUC.

No tralokinumab-related adverse effects, including on cardiovascular function, were observed in cynomolgus monkeys administered tralokinumab by subcutaneous injection at doses of 75, 150, and 300 mg/animal (24.2 to 34.1, 48.4 to 68.2, and 96.8 to 136.4 mg/kg body weight, respectively) once weekly for 13 weeks. At the NOAEL of 300 mg/animal once weekly, the systemic exposure was approximately 57-fold higher than atopic dermatitis adult patients receiving 300 mg of Adtralza Q2W and 49-fold higher than adolescent patients receiving 300 mg of Adtralza Q2W, based on AUC.

Genotoxicity: Genotoxicity studies have not been conducted to evaluate the genotoxic potential of tralokinumab; however monoclonal antibodies are not expected to alter DNA or chromosomes.

Carcinogenicity: Carcinogenicity studies have not been conducted to evaluate the carcinogenic potential of tralokinumab.

Reproductive and Developmental Toxicology: In an enhanced pre- and post-natal development study, intravenous doses of 30 or 100 mg/kg body weight of tralokinumab were administered to pregnant cynomolgus monkeys once every week from the beginning of organogenesis to parturition. No tralokinumab-related adverse effects on embryofetal toxicity, including malformations, or on morphological, functional, or immune function development were observed in the infants from birth through 6 months of age. Thus, the NOAEL for the maternal and developmental toxicity of tralokinumab in this study was 100 mg/kg body weight once weekly (the highest dose tested). At the NOAEL, systemic exposure was 26-fold higher than atopic dermatitis patients receiving 300 mg of Adtralza Q2W, based on AUC. Tralokinumab was detected in infant serum during the post-natal period up until post-natal day 91, but generally not by post-natal 180. This finding demonstrates transport across the placenta.

Effects of tralokinumab on fertility-related parameters were assessed in male and female sexually mature cynomolgus monkeys in separate studies. In the female study, animals were subcutaneously administered tralokinumab at doses of 100 or 350 mg/animal (17.5 to 29.4 mg/kg body weight or 55.6 to 134.6 mg/kg body weight, respectively) once a week for three consecutive menstrual cycles (maximum of 15 doses). In the male study, animals were subcutaneously administered tralokinumab at doses of 200 or 600 mg/animal (22.0 to 39.2 mg/kg body weight or 67.4 to 101.7 mg/kg body weight, respectively) once a week for 13 weeks. No effects on fertility-related parameters, such as reproductive organ weights, menstrual cycle, and sperm analysis were observed. There were also no tralokinumab-related histopathological findings in reproductive tissues (epididymides and testes in males and ovaries, uterus/cervix, and vagina in females). The monkeys were not mated to evaluate fertility. The NOAEL for effects on female reproductive organs was 350 mg/animal and the NOAEL for effects on male reproductive organs was 600 mg/kg (the highest doses tested). At the female and male NOAELs, systemic exposure was 27-fold higher and 24-fold higher, respectively, than atopic dermatitis patients receiving 300 mg of Adtralza Q2W, based on AUC.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrADTRALZA® (tralokinumab injection)

Solution for subcutaneous injection
Single-use pre-filled syringe (150 mg/1 mL)
Single-use pre-filled pen (300 mg/2 mL)

Read this carefully before you start taking **Adtralza** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Adtralza**.

What is Adtralza used for?

Adtralza is used to treat adults and adolescents who have a moderate-to-severe skin condition called 'atopic dermatitis' (eczema) that causes symptoms such as dry, itchy, scaly skin. Adtralza is used for adults and adolescents who cannot be adequately treated using therapies that are applied on the surface of the skin (topical).

Adtralza can be used with or without other drugs called topical corticosteroids (TCS) or topical calcineurin inhibitors (TCIs).

It is not known if Adtralza is safe and effective in children under 12 years old.

How does Adtralza work?

Adtralza contains the active substance tralokinumab.

Adtralza works by stopping a protein in the body called IL-13, which is found in higher amounts in people with atopic dermatitis. This can result in reduced inflammation, improved condition of your skin, and reduced itch, redness and scaling.

What are the ingredients in Adtralza?

Medicinal ingredients: tralokinumab

Non-medicinal ingredients: acetic acid, polysorbate 80, sodium acetate trihydrate, sodium chloride, and water for injection.

Adtralza comes in the following dosage forms:

Adtralza comes as a single-use pre-filled syringe with needle guard, or as a single-use pre-filled pen with needle guard.

Each syringe of Adtralza contains 150 mg of tralokinumab in 1 mL solution (150 mg/mL).

Each pen of Adtralza contains 300 mg of tralokinumab in 2 mL solution (150 mg/mL).

The components of the pre-filled syringe or pre-filled pen are NOT made with natural rubber latex (NRL), dry natural rubber (DNR), or any derivatives (of NRL or DNR).

Do not use Adtralza if:

You are allergic to tralokinumab or to any of the other ingredients of this medicine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Adtralza.

Talk about any health conditions or problems you may have, including if you:

- have eye problems (e.g., itching, redness).
- have a parasitic worm (helminth) infection.
- are scheduled to receive any vaccinations. You should **not** receive a “live vaccine” if you are treated with Adtralza.
- are pregnant or plan to become pregnant. It is not known if Adtralza will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Adtralza will pass into your breast milk and harm your baby.

Other warnings you should know about:

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. **Do not** use Adtralza for a condition for which it was **not** prescribed. **Do not** give Adtralza to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about Adtralza that is written for health professionals.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take Adtralza:

- Your healthcare professional may decide if you or a caregiver can give the injections of Adtralza. **Do not** try to inject Adtralza until your healthcare professional shows you the right way.
- See the detailed “Instructions for Use” that comes with Adtralza for information on how to prepare and inject Adtralza. It also shows how to properly store and throw away used Adtralza pre-filled syringes and used Adtralza pre-filled pens.
- Use Adtralza exactly as your healthcare professional has told you.
- Adtralza is given as an injection under the skin (subcutaneous injection). **Do not** inject into your muscle.
- Your healthcare professional may prescribe other medicines to use with Adtralza. Use the other medicines exactly as your healthcare professional has told you.

Usual dose:

Adtralza is to be injected under the skin (subcutaneously).

Use Adtralza exactly as prescribed by your healthcare professional.

- Your treatment will start with an initial dose (first dose) of **600 mg**. Your initial dose may

be administered by a healthcare professional.

- If using the pre-filled **syringe** this consists of a total of **4** injections.
- If using the pre-filled **pen** this consists of a total of **2** injections.
- Afterwards, a maintenance dose of **300 mg** should be given every other week.
 - If using the pre-filled **syringe** this consists of a total of **2** injections.
 - If using the pre-filled **pen** this consists of **1** injection.
- Your healthcare professional may consider treating you with a maintenance dose every four weeks depending on how you respond to your treatment with Adtralza.

This is a long-term treatment. Your healthcare professional will regularly check your condition to see if the treatment is effective.

Overdose:

There is no specific treatment for Adtralza overdose.

If you think you, or a person you are caring for, have taken too much Adtralza, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, administer the dose as soon as possible. **Do not** wait for the next planned dose. After that, continue dosing at the regular scheduled time. If you are not sure what to do, contact your healthcare professional for guidance.

What are possible side effects from using Adtralza?

These are not all the possible side effects you may have when taking Adtralza. If you experience any side effects not listed here, tell your healthcare professional.

Very rarely, drugs can cause serious side effects, including allergic (hypersensitivity) reactions and anaphylactic reaction. You must look out for signs of these conditions (which can include breathing problems, swelling of the face, mouth, and tongue, fainting, dizziness, feeling lightheaded (low blood pressure), fever, hives, itching, skin rash) while you are taking Adtralza.

If you notice any of the signs above, stop using Adtralza and get emergency help right away.

The most common side effects of Adtralza include:

- Upper respiratory tract infections (i.e., common cold and sore throat)
- Injection site reactions: itching, pain, redness, tenderness, warmth in the area around the injection
- Eye problems: eye inflammation, including redness, swelling, and itching. Tell your healthcare professional if you have any worsening eye problems, including eye pain or changes in vision.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Allergic reactions (hypersensitivity): Breathing problems, difficulty swallowing, swelling of the face, mouth, and tongue, fainting, dizziness, feeling lightheaded (low blood pressure), fever, hives, itching, skin rash			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store Adtralza in its original carton to protect from light. **Do not** put Adtralza pre-filled syringes or Adtralza pre-filled pens into direct sunlight or expose to heat.
- Store Adtralza in a refrigerator between 2°C and 8°C.
 - **Do not** freeze Adtralza pre-filled syringes or Adtralza pre-filled pens. **Do not** use syringes or pens if they have been frozen.
- If necessary, you may keep Adtralza pre-filled syringes or Adtralza pre-filled pens at room temperature up to 30°C for a maximum of 14 days, within the expiration date period of the product.
 - **Do not** store above 30°C.
 - If the carton needs to be removed permanently from the refrigerator, record the date of removal on the outer carton. Throw away syringes or pens in a puncture resistant container if not used within 14 days of storage at room temperature.
 - **Do not** put syringes or pens back in the refrigerator once they have reached room temperature.
- **Do not** shake Adtralza pre-filled syringes or Adtralza pre-filled pens.

- **Do not** use Adtralza after the expiration date shown on the outer box or on the pre-filled syringe or pre-filled pen label. If it has expired, return the whole pack to the pharmacy.
- Keep out of reach and sight of children.

If you want more information about Adtralza:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website www.leo-pharma.ca, or by calling 1-800-263-4218.

This leaflet was prepared by LEO Pharma Inc.

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Last Revised: August 4, 2023

INSTRUCTIONS FOR USE (PRE-FILLED SYRINGE)

PrADTRALZA® (tralokinumab injection)

Solution for subcutaneous injection
Single-use pre-filled syringe (150 mg/1 mL)

Read the following Instructions for Use before you start using Adtralza pre-filled syringes and each time you get a new package. There may be new information. This information does not take the place of talking to your healthcare professional about your medical condition or your treatment.

Keep these Instructions for Use and refer to them as needed.

Each pre-filled syringe contains 150 mg of Adtralza.

Each pre-filled syringe is for single-use only.

IMPORTANT INFORMATION

Important information you need to know before injecting Adtralza:

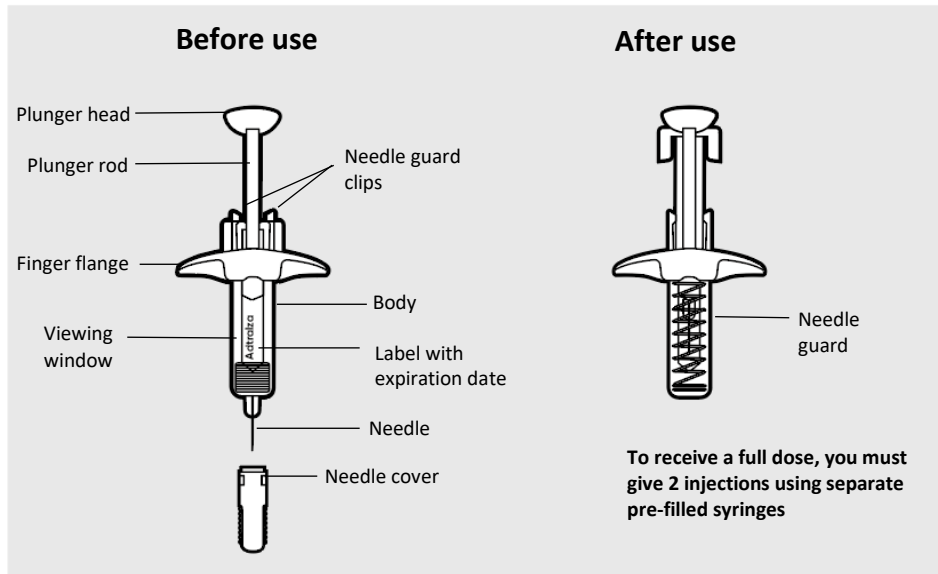
- Your healthcare professional should show you how to prepare and inject Adtralza before you make your first injection.
- **Do not** inject yourself or someone else until you have been shown how to inject Adtralza the right way.
- Talk to your healthcare professional if you have any questions about how to inject Adtralza.
- Each pre-filled syringe has a needle guard that will automatically cover the needle after the injection is finished.
- Inject directly into the fatty layer under the skin (subcutaneous injection only).
- **Do not** remove the needle cover until just before you give the injection.
- **Do not** share or reuse your Adtralza pre-filled syringes.
- **Do not** inject through clothes.

Dosing:

To receive your full dose, you will need more than 1 Adtralza injection.

- Your treatment will start with an initial dose (first dose) of **600 mg**, which is **4** injections. Your initial dose may be administered by a healthcare professional.
- When it is time for your next dose, continue with a maintenance dose of **300 mg**, which is **2** injections.

ADTRALZA PRE-FILLED SYRINGE PARTS:

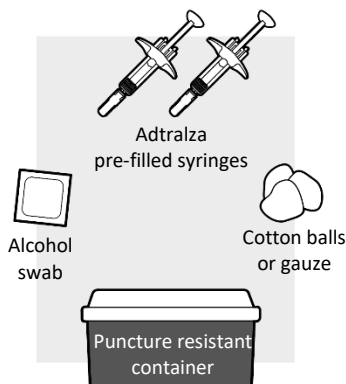


HOW TO STORE ADTRALZA

- Store Adtralza syringes in a refrigerator between 2°C and 8°C.
- Store Adtralza syringes in the original package and protect from light and heat until you are ready to use them.
- **Do not** freeze Adtralza syringes. **Do not** use if they have been frozen.
- Adtralza can be stored at room temperature up to 30°C for up to 14 days, within the expiration date period of the product. Discard syringes if left out of the refrigerator for more than 14 days.
- **Keep Adtralza and all medicines out of the sight and reach of children.**

STEP 1: SETTING UP ADTRALZA FOR INJECTION

1a: Gather the supplies needed for your injections



For each Adtralza dose you will need:

- A clean flat, well-lit work surface, like a table or countertop
- 1 Adtralza carton that contains 2 pre-filled syringes
- An alcohol swab (not included in the carton)
- Clean gauze pads or cotton balls (not included in the carton)
- A puncture resistant (sharps) disposal container (not included in the carton)

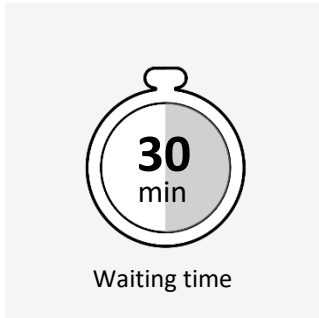
1b: Take the Adtralza carton out of the refrigerator



- **Check the expiry date (EXP) on the carton. Do not** use if the expiry date on the carton has passed.
- Check to make sure the seal on the Adtralza carton is intact. **Do not** use the Adtralza syringes if the seal on the carton is broken.

Do not use the syringes if they have been stored at room temperature for more than 14 days.

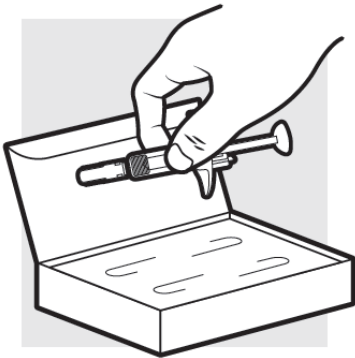
1c: Let the Adtralza pre-filled syringes warm up to room temperature



Set the Adtralza carton on a flat surface and wait 30 minutes before you inject, in order to let the syringes warm up to room temperature (20°C to 30°C). This will help to reduce discomfort and make it easier to inject Adtralza.

- **Do not** microwave the syringes, run under hot water, or leave them in direct sunlight.
- **Do not** shake the syringes.
- **Do not** remove the needle cover on the syringes until you have reached Step 3 and are ready to inject.
- **Do not** put the syringes back in the refrigerator once they have reached room temperature.

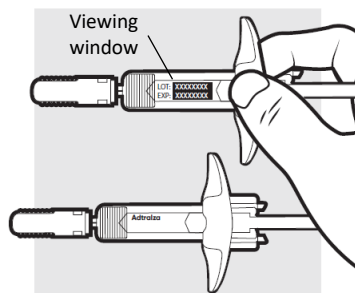
1d: Remove the Adtralza pre-filled syringes from the carton



Remove the 2 Adtralza syringes one by one from the carton by holding the body (not the plunger rod) of each syringe.

- **Do not** touch the needle guard clips to prevent activating the safety device (needle guard) too soon.
- **Do not** remove the needle cover on the syringes until you have reached Step 3 and are ready to inject.

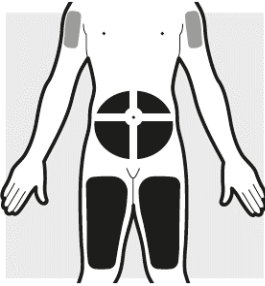
1e: Inspect the 2 Adtralza pre-filled syringes



- Make sure the Adtralza name appears on the syringe labels.
 - Check the expiry date printed on the syringes.
 - Check the medicine through the viewing window. The medicine inside should be clear to slightly pearly and colourless to pale yellow.
 - **Do not** use the syringes if:
 - the expiry date printed on the syringes has passed
 - the medicine is cloudy, discoloured, or has particles in it
 - they look damaged or have been dropped
- In these cases, dispose of the syringes in a puncture resistant (sharps) container and use new syringes.
- You may see small air bubbles in the liquid. This is normal. You do not need to do anything about it.

STEP 2: CHOOSING AND PREPARING THE INJECTION AREA

2a: Choose the area for your injections



- Injection by caregiver only
- Self-injection or by caregiver

- You may inject into:
 - your stomach area (abdomen)
 - your thighs
 - your upper arm. To inject into your upper arm, you will need a caregiver to give you the injections.
- **Do not** inject where the skin is tender, bruised, scaly, scarred, damaged, hard or covered with eczema.
- **Do not** inject within 5 cm of your belly button (navel).
- When administering your dose, make sure each injection is at least 3 cm from the previous injection site and within the same body area.
- **At the time of your next dose, choose a different body area for your set of injections. Do not use the same body area 2 times in a row.**

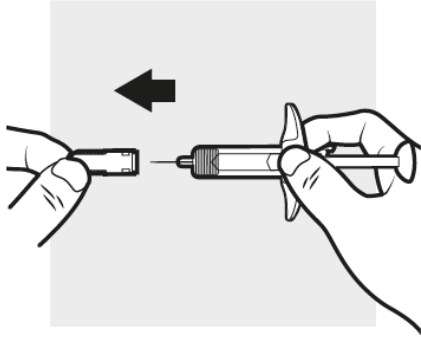
2b: Wash your hands and prepare your skin



- Wash your hands with soap and water.
- Clean the injection area with an alcohol swab using a circular motion.
 - Let the area dry completely.
 - **Do not** blow or touch the cleaned area before injecting.

STEP 3: INJECTING ADTRALZA

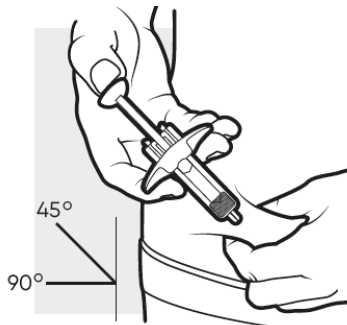
3a: Pull off the needle cover from the pre-filled syringe



Hold the syringe body with one hand, pull the needle cover straight off with your other hand and throw it away in the puncture resistant (sharps) container.

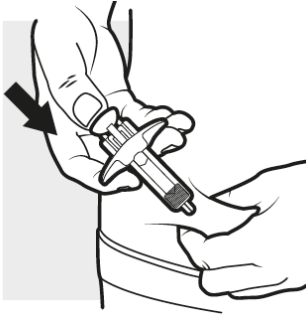
- **Do not try to recap the syringe.**
- **Do not** hold the plunger rod or plunger head while removing the needle cover.
- You may see a drop of liquid at the end of the needle. This is normal.
- **Do not** touch the needle, or let it touch any surface. If either of these occur, throw away the syringe in a puncture resistant (sharps) container and get a new one.

3b: Insert the needle



With one hand, gently pinch and hold a fold of skin where you cleaned the injection area. With the other hand, insert the needle completely into your skin at a 45 to 90 degree angle.

3c: Inject the medicine



Use your thumb to firmly push down the plunger head all the way down. All the medicine is injected when you cannot push the plunger head any further.

3d: Release and remove

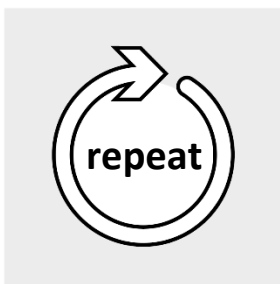


Lift your thumb off the plunger head. The needle will automatically move back inside the syringe body and lock into place.

- Place a dry cotton ball or gauze pad over the injection area for a few seconds. **Do not** rub the injection area. If needed, cover the injection area with a small bandage.
- There may be a small amount of blood or liquid where you injected. This is normal.

Throw away the used syringe in a puncture resistant (sharps) container. **See Step 5** “DISPOSING OF ADTRALZA”.

STEP 4: INJECTING THE NEXT SYRINGE



To get your full prescribed dose, you will need to give more than 1 injection.

- To get your full initial dose of **600 mg**, you will need a total of **4** injections.
- To get your full maintenance dose of **300 mg**, you will need a total of **2** injections.

Get a new syringe and repeat Step 3 for each injection you need to give for your full prescribed dose.

Note

Make sure each injection is at least 3 cm from the previous injection site and within the same body area.

STEP 5: DISPOSING OF ADTRALZA



- Put the used syringes in a puncture resistant (sharps) container right away after use.
 - **Do not** throw away the syringes in your household trash.
- If you do not have a puncture resistant (sharps) container, you can use a container that is:
 - made of heavy-duty plastic,
 - can be closed with a tight-fitting, puncture-proof lid,
 - upright and stable during use,
 - leak-proof, and
 - properly labeled to warn of hazardous waste inside the container.
- When your container is almost full, you will need to follow your community guidelines for the right way to get rid of the container.
- **Do not** recycle your used puncture resistant (sharps) container.

INSTRUCTIONS FOR USE (PRE-FILLED PEN)

PrADTRALZA® (tralokinumab injection)

Solution for subcutaneous injection
Single-use pre-filled pen (300 mg/2 mL)

Read the following Instructions for Use before you start using Adtralza pre-filled pens and each time you get a new package. There may be new information. This information does not take the place of talking to your healthcare professional about your medical condition or your treatment.

Keep these Instructions for Use and refer to them as needed.

Each pre-filled pen contains 300 mg of Adtralza.

Each pre-filled pen is for single-use only.

IMPORTANT INFORMATION

Important information you need to know before injecting Adtralza:

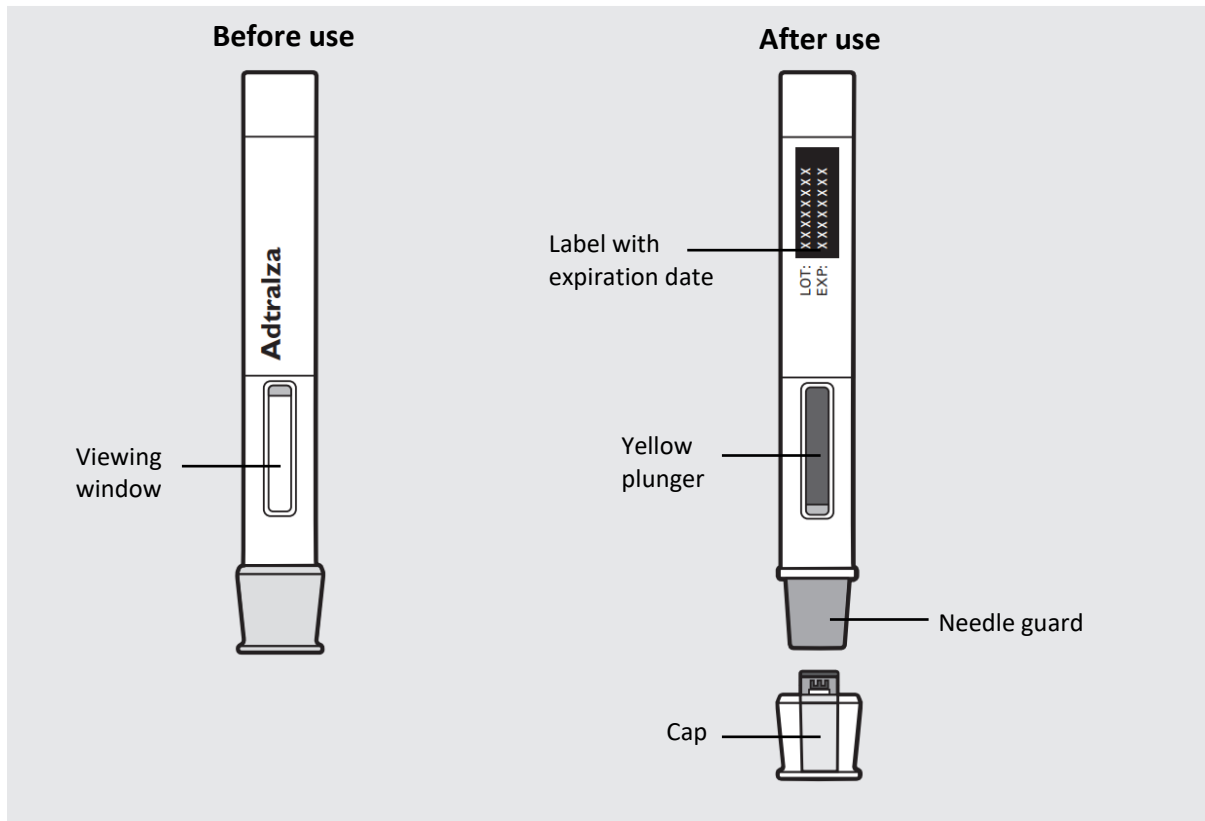
- Your healthcare professional should show you how to prepare and inject Adtralza before you make your first injection.
- **Do not** inject yourself or someone else until you have been shown how to inject Adtralza the right way.
- Talk to your healthcare professional if you have any questions about how to inject Adtralza.
- Each pre-filled pen has a needle guard that will automatically cover the needle after the injection is finished.
- Inject directly into the fatty layer under the skin (subcutaneous injection only).
- **Do not** remove the needle cap until just before you give the injection.
- **Do not** share or reuse your Adtralza pre-filled pens.
- **Do not** inject through clothes.

Dosing:

- Your treatment will start with an initial dose (first dose) of **600 mg**, which is **2** injections. Your initial dose may be administered by a healthcare professional.
- When it is time for your next dose, continue with a maintenance dose of **300 mg**, which is **1** injection.

The instructions below are for a single injection (300 mg). Repeat these steps if you require a second injection (600 mg).

ADTRALZA PRE-FILLED PEN PARTS:

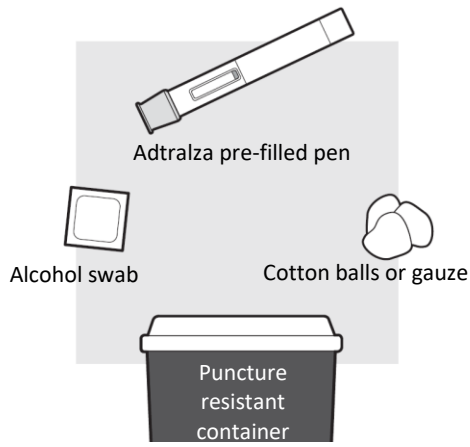


HOW TO STORE ADTRALZA

- Store Adtralza pens in a refrigerator between 2°C and 8°C.
- Store Adtralza pens in the original package and protect from light and heat until you are ready to use them.
- **Do not** freeze Adtralza pens. **Do not** use if they have been frozen.
- Adtralza can be stored at room temperature up to 30°C for up to 14 days, within the expiration date period of the product. Discard pens if left out of the refrigerator for more than 14 days.
- **Keep Adtralza and all medicines out of the sight and reach of children. Contains small parts.**

STEP 1: SETTING UP ADTRALZA FOR INJECTION

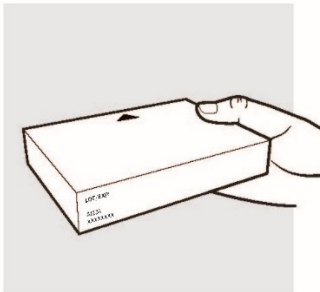
1a: Gather the supplies needed for your injection



For each Adtralza injection you will need:

- A clean flat, well-lit work surface, like a table or countertop
- 1 Adtralza pre-filled pen
- An alcohol swab (not included in the carton)
- Clean gauze pads or cotton balls (not included in the carton)
- A puncture resistant (sharps) disposal container (not included in the carton)

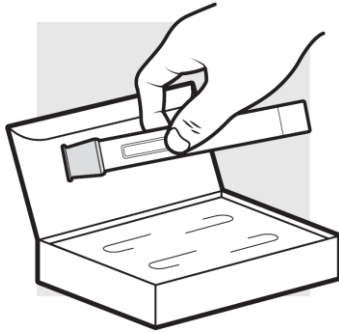
1b: Take the Adtralza carton out of the refrigerator



- **Check the expiry date (EXP) on the carton. Do not** use if the expiry date on the carton has passed.
- When using the first pen, check to make sure the seal on the Adtralza carton is intact. **Do not** use the Adtralza pen if the seal on the carton is broken.

Do not use the pen if it has been stored at room temperature for more than 14 days.

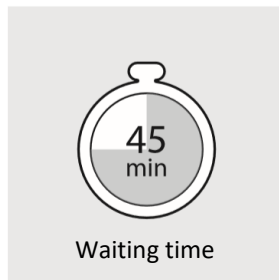
1c: Remove the Adtralza pre-filled pen from the carton



Remove 1 pen from the carton. When using the first pen, put the carton with the remaining pen back in the refrigerator.

- **Do not** remove the cap on the pen until you have reached Step 3 and are ready to inject.

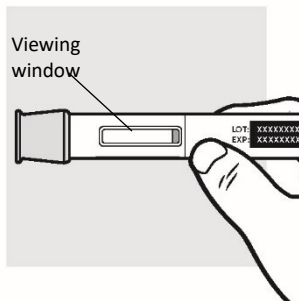
1d: Let the Adtralza pre-filled pen warm up to room temperature



Set the pen on a flat surface and wait at least 45 minutes before you inject, in order to let the medicine warm up to room temperature (20°C to 30°C). This will help to reduce discomfort.

- **Do not** microwave the pen, run it under hot water, or leave it in direct sunlight.
- **Do not** shake the pen.
- **Do not** put the pen back in the refrigerator once it has reached room temperature.

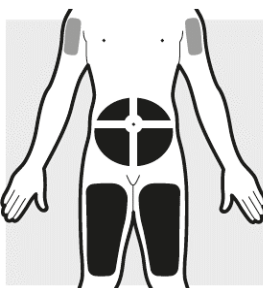
1e: Inspect the Adtralza pre-filled pen



- Make sure the Adtralza name appears on the pen label.
- Check the expiry date printed on the pen.
- Check the medicine through the viewing window. The medicine inside should be clear to slightly pearly and colourless to pale yellow.
- **Do not** use the pen if:
 - the expiry date printed on the pen has passed
 - the medicine is cloudy, discoloured, or has particles in it
 - the product looks damaged or has been droppedIn these cases, dispose of the pen in a puncture resistant (sharps) container and use a new pen.
- You may see small air bubbles in the liquid. This is normal. You do not need to do anything about it.

STEP 2: CHOOSING AND PREPARING THE INJECTION AREA

2a: Choose the area for your injection



- Injection by caregiver only
- Self-injection or by caregiver

- You may inject into:
 - your stomach area (abdomen)
 - your thighs
 - your upper arm. To inject into your upper arm, you will need a caregiver to give you the injection.

- **Do not** inject where the skin is tender, bruised, scaly, scarred, damaged, hard or covered with eczema.
- **Do not** inject within 5 cm of your belly button (navel).
- If administering your initial 600 mg dose (i.e., first dose), make sure the 2 injections are at least 3 cm from one another and within the same body area.
- **At the time of your next dose, choose a different body area for your injection. Do not use the same body area 2 times in a row.**

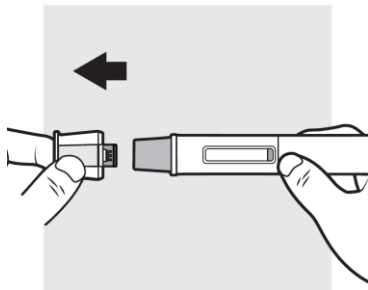
2b: Wash your hands and prepare your skin



- Wash your hands with soap and water.
- Clean the injection area with an alcohol swab using a circular motion.
 - Let the area dry completely.
 - **Do not** blow or touch the cleaned area before injecting.

STEP 3: INJECTING ADTRALZA

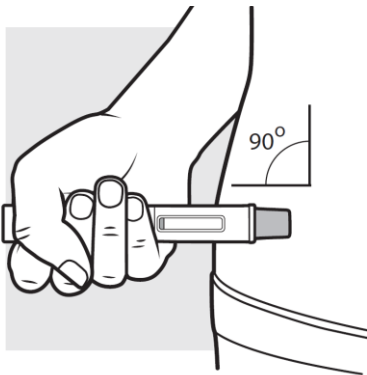
3a: Pull off the cap from the pre-filled pen



Hold the pen with one hand, pull the cap straight off with your other hand and throw it away in the puncture resistant (sharps) container. The needle guard is now exposed. It is there to prevent you from touching the needle.

- **Do not try to recap the pen.** This could cause the injection to happen too soon or damage the needle.
- **Do not** try to touch or push on the needle guard with your finger. This could cause needle stick injury.

3b: Place the pre-filled pen at the injection site so that you can see the window

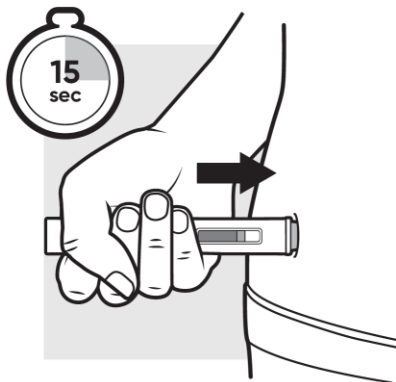


You can gently pinch the skin where you cleaned the injection area or give the injection without pinching the skin.

- Place the needle guard of the pen flat against your skin (90-degree angle) at the injection site you have cleaned. Make sure you can see the viewing window.
- **Do not** change the position of the pen after the injection has started.

If the pen is removed too soon, you may see a stream of medicine coming from the pen. If this happens you may not have received your full dose. Call your healthcare professional.

3c: Press down on the pre-filled pen and hold pressure



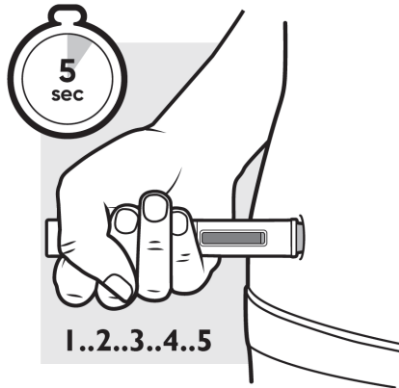
Press the pen down firmly and hold it in place. You will hear a “**click**” to let you know that the injection has started and the yellow plunger will start to move.

The yellow plunger will move to the bottom of the viewing window as the medicine is being injected. **It may take up to 15 seconds to inject the full dose.**

You will hear a second “**click**” when the yellow plunger fills the viewing window.

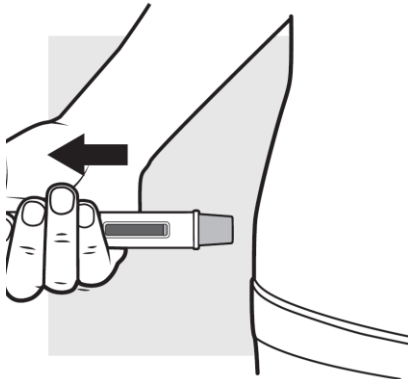
Keep pressing.

3d: Continue to press down for another 5 seconds



After the second “click”, continue to press the pen firmly against your skin for 5 seconds to make sure you get your full dose.

3e: Remove the pre-filled pen



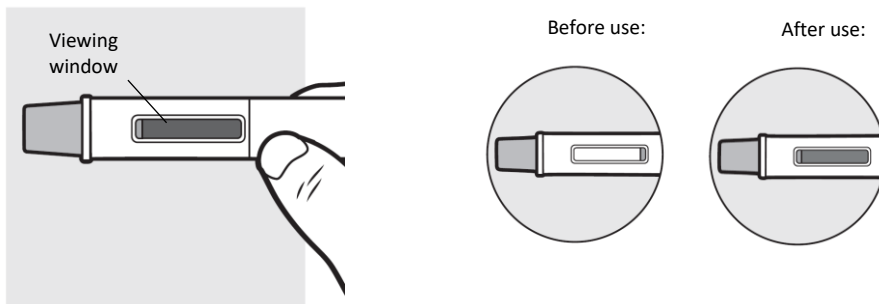
Pull the pen straight away from the injection site. The needle guard will slide down and lock into place over the needle.

Place a dry cotton ball or gauze pad over the injection site for a few seconds.

Do not rub the injection site.

There may be a small amount of blood or liquid where you injected. This is normal. If needed, cover the injection area with a small bandage.

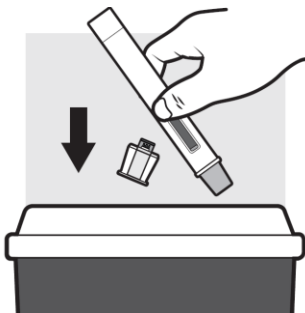
3f: Check the viewing window



Check the viewing window to make sure all the liquid has been injected.

If the yellow plunger does not fill the viewing window you may not have received the full dose. If this happens or if you have any other concerns, call your healthcare professional.

STEP 4: DISPOSING OF ADTRALZA



- Put the used pen in a puncture resistant (sharps) container right away after use.
 - **Do not** throw away the pen in your household trash.
- If you do not have a puncture resistant (sharps) container, you can use a container that is:
 - made of heavy-duty plastic,
 - can be closed with a tight-fitting, puncture-proof lid,
 - upright and stable during use,
 - leak-proof, and
 - properly labeled to warn of hazardous waste inside the container.
- When your container is almost full, you will need to follow your community guidelines for the right way to get rid of the container.
- **Do not** recycle your used puncture resistant (sharps) container.